Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: Implications for selecting patients for carotid angioplasty and stenting

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Objectives: **Carotid angioplasty and stenting (CAS) has been proposed as an alternative to carotid endarterectomy (CEA) in patients excluded from the North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Atherosclerosis Study and in those considered at high risk for CEA. In light of recently released CAS data in patients at high risk, we reviewed our experience with CEA.**

Methods: **The records for consecutive patients who underwent CEA between 1998 and 2002 were retrospectively reviewed, and risk was stratified according to inclusion and exclusion criteria from a "high-risk" or CAS-CEA trial, The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial.**

Results: **Of 776 CEAs performed, 323 (42%) were considered high risk, on the basis of criteria including positive stress test (n = 109, 14%), age older than 80 years (n = 85, 11%), contralateral carotid occlusion (n = 66, 9%), pulmonary dysfunction (n = 56, 7%), high cervical lesion (n = 36, 5%), and repeat carotid operation (n = 27, 3%). Other high-risk criteria included recent myocardial infarction (MI), cardiac surgery, or class III or IV cardiac status; left ventricular ejection fraction less than 30%; contralateral laryngeal palsy; and previous neck irradiation (each <1.5%). Clinical presentation was similar in the high-risk and low-risk groups: asymptomatic (73% versus 73%), transient ischemic attack (23% vs 22%), and previous stroke (4% vs 5%). The overall postoperative stroke rate was 1.4% (symptomatic, 2.9%; asymptomatic, 0.9%). Comparison of high-risk and low-risk CEAs demonstrated no statistical difference in the stroke rate. Factors associated with significantly increased stroke risk included cervical radiation therapy, class III or IV angina, symptomatic presentation, and age 60 years or younger. Overall mortality was 0.3% (symptomatic, 0.5%; asymptomatic, 0.2%), not significantly different between the high-risk (0.6%) and low-risk groups (0.0%). Non-Q-wave MI was more frequent in the high-risk group (3.1 vs 0.9%; $P < .05$). A composite cluster of adverse clinical events (death, stroke, MI) was more frequent in the symptomatic high-risk group (9.3% vs 1.6%; $P < .005$), but not in the asymptomatic cohort. There was a trend for more major cranial nerve injuries in patients with local risk factors, such as high carotid bifurcation, repeat operation, and cervical radiation therapy (4.6% vs 1.7%; $P < .13$). In 121 patients excluded on the basis of synchronous or immediate subsequent operations, who also would have been excluded from SAPPHIRE, the overall rates for stroke (1.65%; $P = .69$), death (1.65%; $P = .09$), and MI (0.83%; $P = .71$) were not significantly different from those in the study population.**

Conclusions: **CEA can be performed in patients at high risk, with stroke and death rates well within accepted standards. These data question the use of CAS as an alternative to CEA, even in patients at high risk. (J Vasc Surg 2004;39:958-66.)**

The safety and efficacy of carotid endarterectomy (CEA) in the treatment of high-grade symptomatic and asymptomatic carotid artery stenosis have been demonstrated in two large-scale prospective randomized trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS).[1-3] These trials included patients who were selected on the basis of good medical risk, long life expectancy, and absence of previous ipsilateral CEA or radiation treatment (ACAS only). A significant portion of patients currently undergoing CEA would, however, be ineligible for the NASCET and ACAS trials, mainly because of advanced age and medical comorbid conditions. This triggered multiple nonrandomized studies, which demonstrated the safety of CEA in a variety of high-risk subsets.[4-6]

Carotid artery angioplasty and stenting (CAS) is an evolving technique for stroke prophylaxis. There are currently no data to support the long-term efficacy of CAS in preventing stroke and death. Short-term clinical outcome of CAS has been the subject of multiple randomized and nonrandomized studies. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE; Cordis Corp, Miami Lakes, Fla) is the first controlled, prospective randomized trial of CAS with a cerebral protection device.[7] Only patients at high risk were enrolled in the SAPPHIRE trial. Preliminary data suggest that CAS with a cerebral protection device, when

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Table I. Criteria for high-risk carotid endarterectomy

High-risk category	*Criteria*
Age (y)	>80
Severe cardiac dysfunction	NYHA class III/IV chronic heart failure
	Left ventricular ejection fraction <30%
	Open heart surgery within 6 weeks
	Myocardial infarction within 4 weeks
	NYHA class III/IV angina
	Cardiac stress test positive for ischemia
Severe pulmonary dysfunction	Chronic oxygen therapy
	pO_2 ≤60 mm Hg
	Baseline hematocrit ≥50%
	FEV_1 or DLCO ≤50% of predicted
Local and anatomic problems	Cervical radiation therapy
	Previous ipsilateral carotid endarterectomy
	C2 or higher carotid bifurcation or division of digastric muscle
	Contralateral carotid occlusion
	Contralateral laryngeal nerve palsy

NYHA, New York Heart Association; *pO_2*, partial oxygen pressure; *FEV_1*, forced expiratory volume in 1s; *DLCO,* diffusing capacity of lung for carbon monoxide; *C2,* second cervical vertebra.

Table II. Criteria for positive cardiac stress test

Exercise stress electrocardiography
Intermediate or high risk Duke treadmill score
Impaired exercise capacity for age and gender
Test-limiting angina
Stress cardiac perfusion scan
Stress-induced reversible perfusion defect or WMA in more than one vessel territory
Baseline ejection fraction ≤40% with stress-induced perfusion defect
Left ventricular enlargement with stress
Increased lung uptake with stress
Pharmacologic or exercise stress echocardiography
Any new WMA with low-dose dobutamine
Stress-induced WMAs in two contiguous segments
Failure of left ventricular systolic cavity to decrease with dobutamine
Angina in conjunction with new WMA
Stress-induced WMA in combination with ejection fraction ≤40%

WMA, Wall motion abnormality.

Table III. Criteria for exclusion

Acute stroke (≤48 h)
Staged elective procedure (within 30 days after CEA)
Elective percutaneous intervention
Contralateral CEA
Other elective operation
Synchronous operation
Common carotid artery angioplasty and stenting or bypass
Cardiac operation
Non-cardiac operation
Intracranial pathology
Intracranial mass
Aneurysm >9 mm
Arteriovenous malformation
Ventriculoperitoneal shunt

CEA, Carotid endarterectomy.

compared with CEA, is associated with a lower incidence of 30-day adverse clinical events, defined as a combined end point of stroke, death, and myocardial infarction (MI).

In this study we report our experience with CEA in SAPPHIRE-eligible patients at high risk.

METHODS

Records for all consecutive patients undergoing CEA performed by members of the Division of Vascular Surgery at the Mayo Clinic, Rochester, Minn, between January 1, 1998, and December 31, 2002, were retrospectively reviewed. Data retrieval and handling were approved by the institutional review board, and were in accordance with the corresponding institutional policy manual. Inclusion and exclusion criteria for this review (Tables I-III) were identical to those used in the SAPPHIRE trial.[4]

Postoperative in-hospital mortality, and ipsilateral and contralateral major stroke rate (functional deficit ≥90 days) and minor stroke rate (functional deficit >24 hours but <90 days) were determined. Formal postoperative neurology consultation was obtained if there was any clinical suspicion of a neurologic event. The frequency of postoperative in-hospital MI was calculated. Major postoperative bleeding was defined as the need for repeat operation. Cranial nerve injuries were classified as major (symptomatic or detectable for >30 days) or minor (asymptomatic and detectable for ≤30 days). Two sets of cardiac isoenzymes (creatinine kinase, troponin) and electrocardiograms were obtained routinely after operation. Patients were routinely dismissed from the hospital on the first postoperative day.

Statistical analysis. The χ^2 or Fisher exact tests, as appropriate, were used to compare proportions between high-risk and low-risk groups. Logistic regression models were used to analyze individual outcome variables (except death, because of low event rate) and combined outcome variables. Univariate logistic regression models were fit for each variable for each outcome. Results are reported with odds ratio, 95% confidence interval for odds ratio, and *P* value. P ≤ .05 was considered significant for all analyses. Multivariate analysis was not pursued for any outcomes, because of low event rate. Some patients underwent more than one CEA; all procedures were included in the analysis, and were treated as independent observations.

RESULTS

Data for patients with concomitant intracranial disease (n = 5), acute stoke (n = 2), and isolated external CEA (n = 3) were not analyzed. Seven hundred seventy-six CEAs (716 patients) were included in the main study. Data for patients (n = 121) who would have been excluded from the SAPPHIRE trial were analyzed separately. Sixty-three percent of the main study population was men; symptoms at presentation included asymptomatic high-grade stenosis in 73%, hemispheric transient ischemic attack in 22%, and stroke with minimal residua in 5%. Three-hundred twenty-three CEAs (42%) were considered high-risk according to

Table IV. Number and frequency of high-risk criteria in all carotid endarterectomies (n = 776)

High-risk criteria	*n*	*%*
Positive cardiac stress test	109	14
Age >80 y	85	11
Contralateral carotid occlusion	66	9
Pulmonary dysfunction	56	7
High carotid bifurcation	36	5
Carotid repeat operation	27	3
LVEF <30%,	11	1.4
NYHA class III/IV CHF	11	1.4
NYHA class III/IV angina	8	1
Cervical radiation therapy	6	<1
Recent (< 6 weeks) cardiac operation	4	<1
Contralateral laryngeal nerve palsy	2	<1
Recent (<4 weeks) MI	1	<1

Eighty-four operations were associated with more than one high-risk criteria.
LVEF, Left ventricular ejection fraction; *NYHA,* New York Heart Association; *CHF,* congestive heart failure; *MI,* myocardial infarction.

criteria presented in Table IV. In 11% of the 776 reviewed cases more than one high-risk criterion was present (two criteria in 9%, three criteria in 1%, four criteria in 1%).

Demographic and clinical data are presented in Table V. Clinical presentation was similar in the high-risk and low-risk groups: asymptomatic (73% vs 73%), transient ischemic attack or amaurosis fugax (23% vs 22%), and previous stroke (4% vs 5%), respectively. Mean age was higher (73 vs 70 years; $P < .0001$), and male sex was more prevalent (67% vs 60%; $P < .05$) in the high-risk group. Cardiovascular risk factors including smoking, arterial hypertension, dyslipidemia, and diabetes mellitus were not statistically different between the high-risk and low-risk groups. Fifty-five percent of the high-risk group and 44% of the low-risk group ($P < .01$) had a history of coronary artery disease (class II angina, previous MI, percutaneous or surgical coronary artery revascularization). Overall, 56% of patients underwent objective cardiac evaluation with a stress test. Cardiac stress tests were performed more commonly in the high-risk group than in the low-risk group (67% vs 47%; $P < .0001$). Nondiagnostic stress tests, those performed more than 6 months before CEA, and those followed by coronary revascularization were not included in the analysis. In addition to routine duplex ultrasound scanning, magnetic resonance angiography and catheter angiography were performed selectively, with catheter angiography used more commonly in the high-risk group (16% vs 11%; $P < .05$).

General anesthesia was used almost exclusively. Intraoperative electroencephalograms were obtained in all cases. Shunting was more frequently necessary in the high-risk group compared with the low-risk group (22% vs 13%; P .001). Fifty-six percent of 66 patients with contralateral carotid occlusion required a shunt. Surgical technique was similar in the high-risk and low-risk groups; standard endarterectomy with patch was used routinely, with eversion

Table V. Demographic data and frequency of clinical variables in patients with high-risk and low-risk CEA

	High-risk (n = 323)	*Low-risk (n = 453)*	P
Presentation			
Asymptomatic (%)	73	73	NS
TIA or amaurosis fugax (%)	23	22	NS
Stroke (%)	4	5	NS
Demographic data			
Mean age (y)	73	70	<.0001
Male gender (%)	67	60	<.05
Cardiovascular risk factors			
Smoking (%)	71	71	NS
Arterial hypertension (%)	88	83	NS
Dyslipidemia (%)	76	81	NS
Diabetes mellitus (%)	24	24	NS
Chronic CAD (%)	55	44	.01
Diagnostic studies			
Cardiac stress test (%)	67	47	.0001
Duplex ultrasound scanning (%)	97	99	NS
MRA (%)	25	22	NS
Angiography (%)	16	11	.05
Operative technique			
Shunt (%)	22	13	.001
Patch (%)	87	89	NS
Eversion CEA (%)	2	3	NS

CEA, Carotid endarterectomy; *TIA,* transient ischemic attack; *CAD,* coronary artery disease; *MRA,* magnetic resonance angiography; *NS,* not significant).

endarterectomy performed in selected cases (Table V). Interposition grafting (four, vein; one, prosthetic) was used in five patients at high risk (two, repeat operation; two, cervical radiation therapy; one, high bifurcation). Intraoperative completion ultrasound scans were obtained in all but two patients. Perioperative β-blockade was used selectively, based on recommendations made at the preoperative medical evaluation.

Ipsilateral and contralateral major and minor stroke rates in patients with symptomatic and asymptomatic disease, at high and low risk, are presented in Table VI. The overall stroke rate in 776 patients was 1.4% (symptomatic, 2.9%; asymptomatic, 0.9%). Three of the 11 strokes were related to acute carotid artery thrombosis, and the others were considered to have an embolic cause. Differences in the stroke rate in symptomatic and asymptomatic patients between the high-risk group (symptomatic, 4.6%; asymptomatic, 0.8%) and low-risk group (symptomatic, 1.6%; asymptomatic, 0.9%) were not statistically significant. Cervical radiation therapy, New York Heart Association class III or IV angina, and symptoms at presentation were associated with a 15.5-fold, 10.8-fold, and 3.3-fold increase in stroke, respectively (Table VII). Patients younger than 60 years had 7.7-fold increased stroke rate, although 80% of these strokes were minor.

Overall mortality was 0.3% (symptomatic, 0.5%; asymptomatic, 0.2%). The difference in mortality between the high-risk group (0.6%) and low-risk group (0.0%) was not significant. The low event rate (n = 2) did not allow

Table VI. Mean frequency (%) of ipsilateral and contralateral stroke in symptomatic and asymptomatic patients with high-risk and low-risk carotid endarterectomy

	High-risk			*Low-risk*			*Any risk*		
	Symptomatic	*Asymptomatic*	*All*	*Symptomatic*	*Asymptomatic*	*All*	*Symptomatic*	*Asymptomatic*	*All*
Ipsilateral									
Major stroke	2.3	0.4	0.9	0.8	0.0	0.2	1.4	0.2	0.5
Minor stroke	2.3	0.4	0.9	0.8	0.9	0.9	1.4	0.7	0.9
Any stroke	4.6	0.8	1.9	1.6	0.9	1.1	2.9	0.9	1.4
Contralateral									
Major stroke	0.0	0.0	0.0	0.8	0.0	0.2	0.5	0.0	0.1
Minor stroke	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Any stroke	0.0	0.0	0.0	0.8	0.0	0.2	0.5	0.0	0.1
Any side									
Major stroke	2.3	0.4	0.9	0.8	0.0	0.2	1.4	0.2	0.5
Minor stroke	2.3	0.4	0.9	0.8	0.9	0.9	1.4	0.7	0.9
Any stroke	4.6	0.8	1.9	1.6	0.9	1.1	2.9	0.9	1.4

further statistical analysis of predictors of postoperative death.

Only non-Q-wave (subendocardial) MIs occurred in the entire series. Postoperative non-Q-wave MI was more frequent in the high-risk group (3.1%) than in the low-risk group (0.9%) ($P < .05$). In addition, a history of coronary artery disease and a positive cardiac stress test were associated with 6.5-fold and 3.5-fold increases in the rate of postoperative non-Q-wave MI, respectively (Table VII). There was a tendency toward more non-Q-wave MIs in patients with contralateral carotid occlusion or with New York Heart Association class III or IV angina.

Differences in the combined major stroke and death rates between the high-risk and low-risk groups were not statistically significant (symptomatic, 3.5% vs 0.8%; asymptomatic, 0.4% vs 0.0%, respectively). A composite cluster of adverse clinical events (death, stroke, MI) was more frequent in the high-risk than in the low-risk symptomatic group (9.3% vs 1.6%; $P < .05$), but not in the asymptomatic group (3.4% vs 2.1%; $P = .36$).

The frequency of other postoperative complications, including major bleeding (1.9% vs 1.1%), acute carotid artery thrombosis (0.6% vs 0.7%), cranial nerve injury (7.1% vs 6.4%), and major cranial nerve injury (1.9% vs 2.0%) was similar in the high-risk and low-risk groups, respectively. Patients with high carotid bifurcation, repeat operations, and previous cervical radiation therapy (local risk factors) had a 7.7% incidence of cranial nerve injury, which was not significantly different from the rest of the population (6.6%). However, there was a trend for more major cranial nerve injuries in patients with local risk factors (4.6% vs 1.7%; $P < .13$).

Further analysis was performed on data for CEAs excluded from the main study (which would have also been excluded from the SAPPHIRE trial). In this population (n = 121, including 26 CEAs combined with open heart surgery, 21 combined with supra-aortic great vessel reconstruction, and 12 bilateral CEAs staged within 30 days) the postoperative rates for stroke (1.65%; $P = .69$), death (1.65%; $P = .09$), MI (0.83%; $P = .71$), stroke and death (3.31%; $P = .25$), and stroke, MI, and death (4.13%; $P = .59$) were not statistically different from the corresponding results in the main study population (n = 776).

Table VII. Odds ratios of predictive factors for postoperative stroke and myocardial infarction at significance level of $P < 0.1$

	Odds ratio	*95% Confidence interval*	P
Stroke			
Age ≤60 y	7.7	2.3-25.7	<.01
Symptomatic presentation	3.3	1-11	<.05
Cervical radiation therapy	15.2	1.6-142.2	<.05
Class III/IV angina	10.8	1.2-96.4	<.05
Myocardial infarction			
Contralateral occlusion	3.0	0.8-11.1	<.1
History of CAD	6.5	1.4-29.0	<.05
Class III/IV angina	8.3	1.0-72.4	<.1
Positive cardiac stress test	3.5	1.1-10.7	<.05
SAPPHIRE high-risk	3.6	1.1-11.5	<.05

CAD, Coronary artery disease; *SAPPHIRE,* Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [trial].

DISCUSSION

NASCET showed that CEA to treat symptomatic stenosis of 70% or greater is associated with a 17% absolute ipsilateral stroke risk reduction at 2 years.[1] An update of this trial confirmed a 6.5% absolute 5-year ipsilateral stroke risk reduction for symptomatic 50% to 69% stenosis, as well.[3] In patients with stenosis of 70% or greater, postoperative mortality was 0.6% and the stroke and death rate was 5.8%, and in patients with 50% to 60% symptomatic carotid artery stenosis, postoperative mortality was 1.2% and the stroke and death rate was 6.7%. In the ACAS, patients with 60% or greater asymptomatic carotid artery stenosis had a 6% absolute stroke and death risk reduction over 5 years, associated with a 2.3% perioperative stroke and death rate, including 1.2% angiography-related stroke rate. When reviewed more carefully, the risk for major stroke and

death, excluding the risk of angiography, was only 0.6%.[2] These landmark studies confirmed the safety and efficacy of CEA in patients with both symptomatic and asymptomatic carotid stenosis.

A population-based study of CEA in patients with symptomatic disease by Hallett et al[5] compared favorably with NASCET, with a 5.1% risk for stroke and death. A retrospective review of 2228 consecutive patients treated at The Cleveland Clinic showed an overall risk for stroke and death of 2.3% (stroke, 1.8%; death, 0.5%) after CEA as an isolated procedure. Patients undergoing combined CEA and coronary artery bypass grafting and those undergoing repeat carotid operations were at significantly higher risk for this combined end point.[8]

For a variety of reasons, patients in the NASCET and ACAS trials were thought to be at low-risk for CEA. Many patients with significant medical comorbid conditions were excluded from these trials, in large part to exclude non-carotid causes of stroke during the follow-up period. These trial exclusions have been used to cast doubt on the validity of the conclusions of the respective trials, that they in fact do not accurately represent the results of CEA in a large number of patients.[9,10] Regardless of where one stands in this argument, there may be a group of patients who are not well-served with CEA. A retrospective review from the Ochsner Clinic found that 46.2% of CEAs in their practice were in patients ineligible for NASCET or ACAS. The difference in major stroke and death rate between trial-eligible (0.5%) and trial-ineligible patients (1.7%) was not statistically significant, perhaps only because of lack of statistical power in the study.[6] In a large retrospective study from The Cleveland Clinic, high-risk status was defined by severe cardiac, pulmonary, or renal dysfunction or by the need for synchronous operations[11] (Table VIII). The rates of postoperative stroke (3.5% vs 1.7%) and death (4.4% vs 0.3%) were significantly greater in the high-risk group. When the combined end point of stroke, death, and MI was evaluated the differences were even greater (7.4% vs 2.9%). Another, smaller retrospective review with similar definitions of high risk failed to demonstrate a difference in rates of stroke (2.0% vs 1.9%) and cardiac complication (3.1% vs 1%) between high-risk and low-risk groups.[4] Similarly, a recent report suggests no difference in the risk for stroke and death between high-risk (1.3%) and low-risk (1.1%) CEAs[12] (Table VIII). Certain anatomic considerations (previous neck irradiation, high lesions, repeat operations) have also been identified as high-risk factors at CEA.

CAS is an evolving technique for treatment of carotid stenosis. Early results of CAS were much inferior to CEA; these results seem to have improved with the introduction of low-profile devices, cerebral protection, and better patient selection.[13] Preliminary results of the SAPPHIRE trial have been released, although they have not yet been subjected to peer review.[7] The 30-day risk for death, stroke, and MI in a group of largely asymptomatic patients was 0.6%, 3.8%, and 2.6%, respectively, in the angioplasty and stenting group, and 2.0%, 5.3%, and 7.3%, respectively, in the CEA group. None of these end points, taken separately, reached statistical significance. The combined 30-day death, stroke, and MI rate was significantly lower in the endovascular arm (5.8% vs 12.6%), however, largely because of the substantial difference in non-Q-wave (subendocardial) MI favoring the endovascular group. In our retrospective review of patients who had undergone CEA the in-hospital risk for death, stroke, and MI was 0.6%, 1.9%, and 3.1%, respectively, in SAPPHIRE-eligible, high-risk patients, which compares favorably to the early results of CAS in the SAPPHIRE trial. SAPPHIRE high-risk status in our experience was associated only with increased postoperative non-Q-wave MI and with corresponding increase in the combined outcome variable, which included MI. An interesting finding in our series was the lack of postoperative transmural MI. This may have been the result of aggressive perioperative β-blockade, which became the standard of care during the study period, or it may be the result of the liberal use of cardiac stress tests in selecting patients for preoperative coronary revascularization.[14] We used general anesthesia almost exclusively; therefore it can be assumed, on the basis of previous reports, that with more frequent use of local anesthesia in selected cases further reduction in cardiac morbidity might be realized.[15]

Using the SAPPHIRE criteria to define high-risk, we found no difference in risk for perioperative stroke and death between high-risk and low-risk groups, regardless of presentation (symptomatic vs asymptomatic). There was, however, a significant difference in the rate of perioperative MI, which was reflected in the combined end point (death, stroke, MI), favoring the low-risk group, but only in symptomatic patients. These findings mirror those of the SAPPHIRE preliminary results; in addition, all MIs in our patients, who routinely had assessment of cardiac isoenzymes postoperatively, were non-Q-wave MIs. The implication of these "chemical" MIs over the long term is uncertain. The lack of any Q-wave MIs in this series seems to justify our practice of routine preoperative cardiac risk stratification based on formal medical evaluation by a cardiologist or vascular medicine specialist and frequent acquisition of cardiac stress tests. When evaluating the local risk factors of repeat operation, high internal carotid lesions, and previous cervical irradiation, there was a tendency toward more major cranial nerve injuries, which did not reach statistical significance; these findings are intuitive.

When looking at a variety of outcome variables, irrespective of SAPPHIRE inclusion or exclusion, we identified several risk factors that did significantly increase the risk for perioperative stroke, including previous cervical irradiation, severe angina pectoris, symptomatic presentation, and age younger than 60 years. Of no surprise, patients with a history of coronary artery disease and positive stress tests were at statistically significant increased risk for perioperative non-Q-wave MI. The increase in postoperative stroke rate in our young ($\leq$60 years) patients is puzzling, even though most of these strokes (80%) were minor. In a statewide analysis of 9918 CEAs the postoperative stroke rate was 1.7% in patients younger than 65 years, which was not significantly different from the older patient cohort.[16]

Table VIII. Definition of high-risk CEA: Major exclusion criteria for NASCET and ACAS, and major inclusion criteria for population-based studies of high-risk CEA and SAPPHIRE

	Exclusion criteria		*Inclusion criteria*			
	NASCET	*ACAS*	*Ouriel et al, 2001*	*Jordan et al, 2002*	*Gasparis et al, 2003*	*SAPPHIRE*
Age (y)	>79	>79			≥80	≥80
History	Contralateral CEA <4 mo	Major surgical procedure <1 mo		Major vascular procedure <1 mo		
	Major surgical procedure <1 mo	Stroke in evolution				
	Stroke in evolution					
Comorbidities						
Cardiac	Unstable angina	Unstable angina	PTCA or CABG <6 mo	Coronary procedure <1 mo	NYHA III/IV	Open heart surgery <6 wk
	Atrial fibrillation	Atrial fibrillation			Canadian CVA heart failure	MI <4 wk
	Valvular heart disease	Valvular heart disease	History of CHF	CABG <6 wk	functional class III/IV	Angina CCS class III/IV
	Symptomatic CHF	Symptomatic CHF		Angina, NYHA III/IV	CABG <6 mo	CHF class III/IV
	MI <6 mo			EF <30%		EF <30%
				MI <4 wk		Abnormal cardiac stress test
Pulmonary	Lung failure	Lung failure with effect on 5-year survival	Severe COPD	FEV_1 <1 L	Steroid dependency	Long-term oxygen therapy
				Home oxygen	Oxygen dependency	Resting pO_2 ≤60 mm Hg
						Baseline hematocrit ≥50%
Renal	Kidney failure	Creatinine >3	Creatinine >3		Creatinine >3	FEV_1 or DLCO ≤50% predicted
Other	Uncontrolled HTN	BP (mm Hg) >180, systolic, >115, diastolic				
	Uncontrolled DM	Fasting glucose >400				
	Liver failure	Liver failure				
	Cancer, <50% 5-year survival	Cancer, <50% 5-year survival				
		Active ulcer disease				
		Warfarin sodium				
Anatomic criteria	Previous ipsilateral CEA	Previous ipsilateral CEA		Previous ipsilateral CEA	Previous ipsilateral CEA	Previous ipsilateral CEA
	Tandem lesion greater than target stenosis	Tandem lesion greater than target stenosis		Cervical radiation treatment	Cervical radiation treatment	Severe tandem lesion
		Cervical radiation treatment		Contralateral carotid occlusion	Contralateral carotid occlusion	Cervical radiation treatment
						Contralateral carotid occlusion
				High cervical lesion	High cervical lesion	High cervical lesion (at least C2)
				Lesion below clavicle		Lesion below clavicle
						Contralateral laryngeal palsy

CEA, Carotid endarterectomy; *SAPPHIRE,* Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [trial]; *CHF,* chronic heart failure; *MI,* myocardial infarction; *HTN,* hypertension; *DM,* diabetes mellitus; *BP,* blood pressure; *PTCA,* percutaneous transluminal coronary angioplasty; *CABG,* coronary artery bypass graft; *COPD,* chronic obstructive pulmonary disease; *NYHA,* New York Heart Association; Canadian *CVA,* Canadian Cardiovascular Association; *CCS,* Canadian Cardiovascular Society; *EF,* ejection fraction; pO_2, partial oxygen pressure; FEV_1, forced expiratory volume in 1 s; *DLCO,* diffusing capacity of lung for carbon monoxide; *C2,* second cervical vertebra.

We hypothesize that very young patients with critical carotid artery disease may represent a population with premature atherosclerosis, unrecognized hypercoagulable disorders, or labile plaques predisposing to postoperative embolic complications. Carotid stenosis in these patients may simply be a marker for more severe atherosclerosis seen in young patients. At the other end of the age spectrum, patients older than 80 years did not demonstrate increased risk for postoperative stroke and death in this series.

Contralateral carotid artery occlusion did not have a significant effect on postoperative stroke and death in our experience. CEA with liberal use of selective shunting resulted in similar excellent outcome in earlier studies, as well.[17,18]

The long-term benefit of carotid artery revascularization in asymptomatic patients at high medical risk is controversial. The relatively modest reduction in stroke risk in ACAS, which became apparent only after 5 years, suggests that asymptomatic patients with limited survival may not enjoy any benefit. Stroke risk reduction increased with the severity of stenosis in NASCET, but not in ACAS.[1,2] As such, for patients at prohibitive medical risk we typically recommend CAS for critical carotid stenosis in asymptomatic patients and for symptomatic patients who have failed medical therapy. Patients with limited life expectancy are frequently treated expectantly, especially if they have asymptomatic disease.

Although this series represents a consecutive group of patients undergoing CEA, its limitations are related to its retrospective nature. Postoperative complication rates are in-hospital values, which may be lower than 30-day results. Without an evaluation by an independent neurologist, the recognition of cerebrovascular events, minor events in particular, remained subjective and dependent on variations in the scrutiny of the postoperative examination. Similarly, minor cranial nerve injuries may have been missed or subjectively misinterpreted. Another source of variation is that perioperative care changed during the study period as perioperative β-blockade became more popular. Direct comparison of our results with those of the SAPPHIRE trial is limited by the possible differences in the distribution of individual high-risk criteria in the two studies. Our population had a somewhat higher percentage of patients without symptoms, compared with the SAPPHIRE trial (73% vs 66%). In addition, some inclusion criteria for SAPPHIRE eligibility, such as advanced age and contralateral carotid occlusion, may not have a significant effect on immediate postoperative outcome.

CONCLUSION

CEA can be performed with very low morbidity and mortality, even in SAPPHIRE-eligible patients at high risk. In the setting of surgical results such as these, the role of CAS in patients at high risk remains undefined. When taken in aggregate, the SAPPHIRE criteria are not predictive of perioperative stroke; they are predictive of perioperative non-Q-wave MI. When evaluating the combined end point of stroke, death, and MI, patients at high risk with symptomatic disease are at increased risk, largely on the basis of increased risk for non-Q-wave MI; patients with asymptomatic disease are not. Patients with local risk factors (repeat operation, high bifurcation, radiation therapy) tend to have more major cranial nerve injuries.

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DISCUSSION

Dr Dennis Fry (Iowa City, Ia). I just have two questions. First, you said that you do stress tests in all your patients. Does that change your approach in the 35% of symptomatic patients? For instance, do they go to coronary bypass or do they go to angioplasty and stenting before undergoing carotid endarterectomy? And then my second question, which is more of a comment, is that there was an article recently by Kim et al in *Circulation* in 2002, and they stated there was a sixfold increase in mortality for non-Q-wave MIs, and it sounded like you were suggesting that non-Q-wave MIs didn't matter that much.

Dr Geza Mozes. Regarding the first question, one of the inclusion criteria in the SAPPHIRE trial was having a preoperative positive stress test; therefore, in this study, in the high-risk group, we included only those patients with a positive stress test who did not have an intervention between the positive stress test and the carotid endarterectomy. If the cardiac stress test is highly positive, then our patients routinely undergo percutaneous coronary revascularization.

The other question recalls a very, very important issue, and comes up repeatedly in this discussion. One thing we have to ask at first is, Do you think that having a subendocardial MI is the cause of a future death, or is it just an indicator, a sort of stress test, that points to a population with poor cardiac prognosis?

Dr Iraklis Pipinos (Omaha, Neb). This is certainly important data that will influence our daily decision-making. The SAPPHIRE trial reported a significantly higher non-Q-wave MI rate in their patients having carotid endarterectomies. Of interest, it was that higher rate, around 5% to 6%, that made their 30-day combined death, stroke, and MI rates significantly worse in the endarterectomy patients compared with the patients receiving angioplasty and stenting. What do you think accounts for the difference between their non-Q-wave MI rate and the one you observed in your series?

Dr Mozes. It is a good question. First of all, one should assume in this retrospective study that we may have overlooked a few minor events. However, I mentioned during the talk that it is our policy to check troponin after every single endarterectomy; therefore our sensitivity may have been quite reasonable. I don't have a good explanation why our results are better. We follow usual rules by applying aggressive β-blockade and extensive preoperative cardiac workup. Also, when you take numbers from two different studies it is very difficult to compare them face to face. The SAPPHIRE trial was a relatively small study, so what we are seeing here may be just a statistical variation.

Dr Donald Jacobs (St Louis, Mo). I would take a different bent on your data, to say that you just have reaffirmed the findings of the SAPPHIRE trial, that is, these patients do have increased risk for non-Q-wave MI. Whether that is significant or not could be debated. Also, the risk of stroke, although statistically not different, may be a number that would be significant in larger numbers, a larger study. I think that again they are not that different, the high-risk stroke rate in your hands and the ones that were in the SAPPHIRE trial. I'm not sure I would take the same approach that shows that these patients are not at high risk. But indeed there is a difference, and the results are not that greatly different from the SAPPHIRE data. I wonder what your comments are on that.

Dr Mozes. I agree that there are several different ways to look at the same set of data. The question is, Where do you want to put the emphasis? I think that we should emphasize that SAPPHIRE-eligible status should not necessarily be an indication for carotid artery stenting. What we suggest is that it would not be correct to submit 42% of the whole population to carotid artery stenting, based on the preliminary data of the SAPPHIRE trial. On the other hand, I agree that if we look at the symptomatic high-risk patients, which is a much smaller population, about 15% of the entire population, then you can make an argument that those patients, at least in the short run, will do better with stenting. Indeed, that pretty much describes our practice; in addition to the patients with local risks, the patients who are symptomatic and have very high medical risk are those to whom we recommend stenting. Again, if you put all of these numbers together, that will be about 15% of the population, and not 42%. This is the point of this study.

Dr Timothy Sullivan. I would just like to make a brief comment, as the senior author of the paper, that the idea is not to condemn carotid angioplasty and stenting. Simply stated, perhaps we need to raise the bar a little bit in terms of comparing angioplasty and stenting in high-risk patients with endarterectomy in high-risk patients. The idea is not that angioplasty and stenting has to meet a standard of 6% risk for stroke and death in symptomatic patients, and 2% or 3% in asymptomatic patients, but in fact the bar is substantially higher than that. Carotid endarterectomy remains the gold standard for most patients, whether high or low risk.

INVITED COMMENTARY

John J. Ricotta, MD

In an ongoing effort to refine indications for carotid endarterectomy (CEA), multiple investigators have attempted to define "high-risk" subgroups in which the outcomes of CEA are worse than generally expected. The hypothesis has been that carotid artery stenting (CAS) would be preferable in such patients. The SAPPHIRE trial, completed in 2002 but not yet published, is an effort to test this hypothesis in a prospective randomized trial. Results, presented in abstract form, are sobering for advocates of CEA and CAS alike.

In this issue of the JVS, Mozes et al present the latest of several single-institution retrospective reviews in which patients were divided into normal- and high-risk categories on the basis of criteria used in "high-risk" trials such as SAPPHIRE.[1-3] Their results, like those of other surgical series, fail to show different outcomes